REMARKS

Claims 1, 5, 10, 14, 18, 22, 26, 31, 33, 37, 40, and 42 have been amended herein. Claims 1, 10, 18, 26, 33, and 40 have been amended to recite that the method uses an RNase inhibitor protein in a buffer that is devoid of reducing agents. Claims 5, 14, 22, 31, 37, and 42 have been amended to address the claim objection noted at the top of page 3 of the Office Action.

Claims 1-45 remain in the application. Favorable reconsideration is respectfully requested.

Election/Restriction:

Applicants thank Examiner Hutson for withdrawing the prior restriction requirement.

Rejection of Claims 1-45 Under §112, First Paragraph (Written Description):

This rejection is respectfully traversed.

Applicants explicitly traverse the statement made at page 3, last paragraph of the Office Action. Here, the Office states:

> Claims 1-45 are directed to all possible methods of protecting and storing RNA or performing RT-PCR comprising the claimed combination of RNase inhibitors, DTT, and heat.

The quoted statement does not accurately reflect the positive language of independent claims, either as originally submitted or as amended herein. The present claims are a series of verbs; that is, a series of positively recited steps. Thus, the claims simply cannot encompass "all" possible methods utilizing RNase inhibitors, DTT, and heat. Such a broad interpretation would require the Office to ignore all of the verbs (*i.e.*, all of the positive elements) contained in the claims. (Also, due to the present amendment, the claim set now explicitly excludes the presence of a reducing agent, including DTT, in the buffer solution in which the RNase inhibitor protein is disposed.)

Second, the above-quoted passage ignores a host of positive limitations that appear in the claims. For example, the claims do not recite any and all "RNase inhibitors." Rather,

each of independent Claims 1, 10, 18, 26, 33, and 40 uses the positive phrase "RNase inhibitor **protein**." Thus, the positive wording of the claims requires that the RNase inhibitor be a protein.

Similarly, the claims do not encompass any random application of heat. Rather, each of claims 1, 10, 18, 33, and 40, places a positively recited lower limit (50°C or 55°C) on the temperature applied to the solution. The claims also positively recite when (and for how long) the heat should be applied.

Thus, Applicants traverse this rejection on the basis that the Office is ascribing an unreasonably broad interpretation to the scope of the claims.

Specifically addressing the nature of the RNase inhibitor protein, the Office has taken the position that "The specification... only provides those methods encompassing the use of ... heat, and either rat or human RNasin...." See page 3, last paragraph of the Office Action. In support of this conclusion, the Office makes two points: (1) there is no disclosure of a structure-to-function relationship in the disclosed species of RNase inhibitor proteins; and (2) the specification "fails to describe any additional representative species of RNase inhibitor proteins for use in the claims methods...." Applicants traverse this grounds of rejection as being clearly improper because the specification contains a detailed description, including prior art reference citations, of human, pig, and rat RNase inhibitor proteins. In particular, the Office's attention is directed to the present specification, at page 4, second full paragraph, to page 5, first full paragraph:

> RNase inhibitor proteins were first identified as a protein that inhibited pancreatic RNase. This family of RNase inhibitor proteins was identified and purified from placental extracts. (See Blackburn, P. et al. (1977) *J. Biol. Chem.* 252:5904-5910.) A gene for an RNase inhibitor was subsequently cloned from the placenta, and a recombinant RNase inhibitor protein developed. (See, for example, U.S. Patent 5,552,302, to Lewis et al.) These inhibitor proteins function mechanistically by forming a very strong 1:1 complex between the inhibitor and the RNase.
>
> The genes encoding the human placental inhibitor, as well as those from pig and rat, have been cloned and sequenced. The three-dimensional structures for some of the members of the family have also been determined. (See Kobe & Deisenhofer (1996) "Mechanism of ribonuclease inhibition by ribonuclease inhibitor protein based on the crystal structure of its complex with ribonuclease A," *J. Mol. Biol.* 264(5):1028-1043.) Comparisons of the properties of this family of RNase inhibitor proteins have been published. (See Blackburn et al. (1977) *J. Biol. Chem.* 252:5904-

5910; Burton & Fucci (1982) *Int. J. Pept. Protein Res.* 19:372-379.) The usefulness of these inhibitor proteins in molecular biology applications has resulted in their characterization to some extent. In particular, the human placental form of the inhibitor protein has been reported: (1) to inhibit RNases of the RNase A, B and C family of enzymes; (2) to be thermally inactivated at about 55°C in aqueous solution; and (3) to be unable to inhibit the major RNase from *E. coli* (commonly referred to as RNAse 1) or RNases from plant sources. (See, for example, "Expressions 9.3," a publication of Invitrogen Life Technologies (San Diego, California) that describes Invitrogen's RNaseOUT-brand inhibitor. See also Ambion, Inc.'s (Austin, Texas) product literature for Ambion's RNase Inhibitor.) When the RNAse is complexed to the inhibitor, the complex does not have any RNAse activity. However, as reported in the above-noted product literature, the RNAse is not permanently inactivated by the inhibitor. If the inhibitor is released from the inhibitor-RNase complex, under certain conditions the freed RNAse will regain its ability to degrade RNA.

The RNase inhibitor protein from human placenta——either isolated from its native source or made through recombinant means——has been available commercially for a number of years. During that time, reports have been published that the inhibitor is ineffective in preventing RNA degradation in certain molecular biology applications, such as RT-PCR. This is due, reportedly, to the poor thermostability of the inhibitor protein at the temperatures used in such reactions. In fact, these publications suggest that adding the RNase inhibitor would be detrimental to successful completion of RT-PCR experiments. In short, the product literature suggests that the RNase inhibitor protein as supplied may already have a significant fraction of the inhibitor protein complexed to RNase. Further, this RNAse would then be released in an active form upon heating of a solution containing the RNase inhibitor. The literature goes on to infer that the potentially active RNAse released may destroy the RNA template in the experiments, thus leading to failure in the experiments.

In short, a host of different RNase inhibitor proteins (from human and non-human origins) are known in the art, a fact that is clearly noted in the application as filed. RNase inhibitor proteins can be purchased commercially from several companies, including Promega, Ambion, Eppendorf, New England BioLabs, Qbiogene, Krackeler Scientific, and many others. See Exhibits A, B, C, D, E, and F (respectively) attached hereto and incorporated by reference. These exhibits are screen shots from the web pages of the listed commercial suppliers of RNase inhibitor proteins.

The class of inhibitor proteins recited in the claims do share an important structural characteristic: they must be proteins (a positive recitation that appears in all of the claims). They also must be capable of inhibiting RNase. On this issue, Applicants note that a patent application is not aimed at a casual reader. It is aimed at a person of ordinary skill in the art.

In this case, a person of ordinary skill would be a Ph.D.-level researcher with a working knowledge of RT-PCR. Because limiting the RNase-mediated degradation of template RNA is a pervasive problem when attempting RT-PCR, an ordinarily skilled artisan is very, very familiar with compounds and protocols used to inhibit the action of RNases. Thus, one of skill in the art is perfectly capable of determining whether or not a protein (any protein) is capable of inhibiting RNase. All that needs to be done is to run two side-by-side RT-PCR reactions in a reaction solution known to contain RNase: one reaction includes the putative inhibitor protein, one reaction does not. If the inhibitor protein functions to inhibit the RNase, the reaction containing the inhibitor protein will yield a specific amplification product. Otherwise, it will not (because the RNase will degrade the RNA template).

The MPEP and the case law are clear with respect to the written description requirement. All that is required is that the specification reasonably conveys to the artisan that the inventor had possession of the invention at the time the application was filed. See, for example, *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 227 USPQ 177, 179 (Fed. Cir. 1985) and MPEP §2163.02. The subject matter in the claims **does not** need to be described literally (*i.e.*, in haec verba) in the specification. (That being said, the recitation contained in Claims 5, 14, 22, 31, 37, and 42 appears almost literally in the specification as filed.)

Applicants further traverse this rejection because defining a generic term (RNase inhibitor protein) by listing a number of exemplary species that fall within the generic term is a perfectly valid and **approved** approach to defining a generic term. See MPEP §2164.08 and *In re Marzocchi*, 169 USPQ 367, 370 (CCPA 1971): "How a teaching is set forth, **by specific example** or broad terminology, is not important." (Emphasis added.)

Thus, in the present application, the specification clearly discloses human-derived RNase inhibitor proteins (both native and recombinant), rat-derived RNase inhibitor proteins, and porcine-derived RNase inhibitor proteins. (See the above-quoted passage.) All of these types of proteins, as well as others, **are commercially available products**. See Exhibits A, B, C, D, E, and F. Applicants therefore respectfully submit the specification provides a reasonable amount of information to convey to a person of ordinary skill in the art that Applicants were in possession of the invention at the time the application was filed.

Applicants therefore submit that the rejection of Claims 1-45 under §112, first paragraph, written description, is untenable. Withdrawal of the rejection is requested.

Rejection of Claims 1-45 Under §112, First Paragraph (Enablement):

As applied to Claims 5, 14, 22, 31, 37, and 42, Applicants submit that this rejection is untenable because these claims recite that the RNase inhibitor protein is derived from porcines, rats, human placentas, or recombinant sources of human placental proteins. Each of these sources of RNase inhibitor proteins is explicitly described in the specification as filed. (See the large quoted passage from the specification in the previous section of this response.) These types of RNase inhibitor proteins are commercially available products. (See Exhibits A, B, C, D, E, and F, attached hereto.) Because these products can be purchased commercially, the person of ordinary skill in the art can simply purchase the recited inhibitor proteins. Thus, as applied to Claims 5, 14, 22, 31, 37, and 42, Applicants respectfully submit that the rejection under the enablement clause of §112, first paragraph is clearly improper.

As applied to the remaining claims, this rejection is traversed.

Specifically addressing the comments made in the Office Action, Applicants again note that it appears that the Office is ascribing an unreasonably broad interpretation to the claims. Most notably, at the top of page 5 of the Office Action, first full paragraph, the Office states:

> Claims 1-45 are so broad as to encompass <u>any</u> method of protecting and storing RNA or performing RT-PCR comprising the claimed combination of DTT and heat and any RNase inhibitor protein.

This simply cannot be the case. This interpretation ignores the positive limitations of the claim language itself. For example, as noted previously, the claims do not encompass any random application of heat. Rather, each of claims 1, 10, 18, 33, and 40, places a positively recited lower limit (50°C or 55°C) on the temperature applied to the solution. The claims also positively recite when (and for how long) the heat should be applied. The claims have been amended herein to exclude the presence of reducing agents in the buffered solution that contains the RNase inhibitor protein. Applicants therefore traverse this rejection on the basis that the Office is ascribing an unreasonably broad interpretation to the scope of the claims.

Specifically regarding the RNase inhibitor protein, there is no reason a person of ordinary skill in the art cannot practice the invention using any RNase inhibitor protein, now known or discovered in the future. A host of such proteins are now commercially available, as evidenced by the attached Exhibits. The person of ordinary skill in the art does not need to know anything at all about the protein, other than that it functions as an RNase inhibitor protein. That is all that the claims require. If the protein is an RNase inhibitor protein, it can be used in the claimed invention.

The Office Action contains a rather lengthy discussion of structure/function relationships, knowledge and guidance of which amino acids in the protein's sequence are critical or conserved, amino acid substitutions, tolerance to modification, etc. Applicants respectfully submit that this entire discussion is irrelevant to the issue of enablement. The person of ordinary skill in the art can be completely, utterly and totally **ignorant of the structure of the RNase inhibitor protein** and still be fully capable of practicing the invention as broadly as it is claimed. For that matter, the person of ordinary skill in the art does not even have to know that the RNase inhibitor is a protein at all. For the commercially available RNase inhibitors, all the person of ordinary skill in the art needs to do is buy the inhibitor.

It is well-settled law that the Applicants **do not** have to have any knowledge whatsoever of **how** an invention functions. All Applicants have to do is show that the invention does work. Thus, the entire discussion contained in the Office Action regarding the structure of the RNase inhibitor protein is irrelevant. Applicants do not have to elucidate, nor do they have to claim, the underlying biological phenomenon by which the claimed invention operates. Again, the person of ordinary skill in the art can practice the invention without any knowledge whatsoever about the amino acid sequence of the RNase inhibitor protein.

Moreover, Applicants respectfully submit that Office has not properly presented a *prima facie* finding of lack of enablement. The Office has the burden of providing sound scientific reasons, supported by the record, *why* the specification fails to properly enable the claims. (See, for instance, *In re Angstadt*, 190 USPQ 214 (CCPA 1976).) As part of that burden, the Office must present evidence showing that the disclosure requires **undue** experimentation. (*Id.* at 219.) The key concept of non-enablement is "undue," not "experimentation." In short,

satisfaction of the enablement requirement of §112 is not voided by the necessity for some experimentation, such as routine screening. (*Id.*) A considerable amount of experimentation is permissible if it is routine or if the specification provides a reasonable amount of guidance with respect to how the experiments should proceed. (See also *In re Jackson*, 217 USPQ 804 (Bd. App. 1982).)

In the present situation, a host of RNase inhibitor proteins are already known in the art and commercially available. Any of them will work. Some will work better than others. But there is no requirement in the patent law that all of the individual species falling within a generic term function with equal success. See, for example, *In re Gardner*, 177 USPQ 396 (CCPA 1973).

In the case of a newly discovered RNase inhibitor protein, the entire discussion contained in the Office Action still remains irrelevant. A person of ordinary skill in the art is perfectly capable of doing a routine RT-PCR test reaction according to the present invention, and thereby determine whether RNases present in the reaction cocktail have been inhibited. Again, routine experimentation does not constitute undue experimentation under the controlling law. Applicants also note that the empirical and often unpredictable nature of the RT-PCR protocol is notoriously well known. See, for example, Exhibit G, which is a brief primer on how to become "an effective PCR'er." Exhibit G is taken from the web site of Dr. Jack Vanden Heuvel of Penn State University, Departments of Veterinary Science and Molecular Toxicology. The last full paragraph of page 4 of Exhibit G is particularly enlightening:

> The last item required to be a good PCR'er is patience. This technique is very sensitive to timing (how quickly reactions are assembled), season (summers are often prone to crashes), various forms of contamination and intermittent bouts of stress and tedium. After a series of failures, it is often best to walk away from PCR and indulge in your favorite vices for a period of time. **Although PCR is considered science, (it is simply a glorified enzyme assay), there is a lot of art involved and a little luck never hurts either. Learn the basics and cross your fingers**.

(Emphasis added.) Adjustment of primer concentrations, stringency, cycling conditions, RNase inhibitor protocols, etc, are all part of the routine nature of the RT-PCR. Modifying these parameters to suit a given application is not undue experimentation at all, but is an

unavoidable and routine aspect of the everyday practice of the RT-PCR. Moreover, none of these considerations requires any knowledge at all about the amino acid sequence of the RNase inhibitor protein.

Like the written description requirement, the enablement requirement also takes into account the knowledge that can be attributed to the practioner of ordinary skill in the art. Thus, "not everything necessary to practice the invention need be disclosed" to enable the claimed invention. See MPEP §2164.08. Precedential case law from the Federal Circuit also explicitly holds that "what is well-known is best omitted" from the specification. See *In re Buchner*, 18 USPQ 2d 1331, 1332 (Fed. Cir. 1991). All that is required to satisfy the enablement requirement is that one of skill in the art can practice the invention. The specification **does not** have to disclose each and every permutation possibly encompassed by the claims. Again, see MPEP §2164.08. On this issue, the Court of Customs and Patent Appeals (the predecessor to the Federal Circuit) has held (in a precedential opinion) that the scope of the specification must bear only a "reasonable correlation" to the scope of the claims. See *In re Fisher* 166 USPQ 18, 24 (CCPA 1970). The specification discloses a host of RNase inhibitor proteins, a large number of which are commercially available. Having done so, a person of ordinarly skill in the art can use his or her storehouse of knowledge to make any **routine** adjustments to make the invention work using any other RNase inhibitor protein.

For the above reasons, Applicants respectfully submit that the rejection of Claims 1-45 under 35 U.S.C. §112, first paragraph, enablement is untenable. Applicants therefore respectfully request that this rejection now be withdrawn.

Rejection of Claims 1-45 Under §103(a) Over Murthy et al. (1992) Biochem J. 281:343-348, in View of WO 00/17320 ("Ambion"):

This rejection is believed to have been overcome by amendment to independent Claims Claims 1, 10, 18, 26, 33, and 40. These claims have been amended to recite that the method uses an RNase inhibitor protein in a buffer that is devoid of reducing agents. Both the Murthy et al. paper and the Ambion PCT publication require the use of the reducing agent DTT. The

present claims, however, exclude using a reducing agent in the buffer that contains the RNase inhibitor protein.

Applicants therefore submit that the rejection of Claims 1-45 under 103(a) over Murthy et al. in view of WO 00/17320 has been overcome. Withdrawal of the rejection is respectfully requested.

Applicants submit that the application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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